Male Fertility Preservation: How far are we from the Clinics?

Stefan Schlatt*, Swati Sharma

Centre of Reproductive Medicine and Andrology, Institute of Reproductive and Regenerative Biology, Münster Germany

DESCRIPTION

Male factor infertility contributes to nearly half of the failed conception and pregnancy attempts. The primary reason attributed in adult males is constant decline in semen quality and sperm count during the past 50 years due to various known and unknown causes [1]. Adult patients producing mature gametes (fertilization competent spermatozoa) have the option to cryopreserve semen for future ART treatments.

In contrast, there is a big cohort of adult infertile men like azoospermic patients and prepubertal boys undergoing cytotoxic treatment or genetic abnormalities like Klinefelter’s syndrome, who do not produce mature gametes and do not have any option to father their biological children in the future. However, due to availability of advanced cancer therapies and treatment options, the survival rate of such prepubertal cancer patients is over 85%, but infertility leads to a decline in their overall quality of life [2].

Since cryo-banking of human pre-pubertal testicular tissue was initiated prior to administering cancer therapies, researchers are contemplating on identifying and establishing effective strategies which can be employed for clinical fertility preservation [3].

There are several cell-based and tissue-based experimental ex vivo approaches (iPS-cell based, spermatogonial stem cell-based, 2D- or 3D-organoid and tissue-based strategies) currently being developed to achieve complete spermatogenesis in primates [4-6]. Most of these in vitro approaches like spermatogonial stem cell culture or tissue culture are neither well-established nor can they yet be considered safe and efficient to initiate clinical applications. Currently, testicular grafting and germ cell transplantation are the only two strategies which can be applied for fertility preservation in primate models and have been validated in monkeys [7-9].

The risk of reintroducing or auto-transplanting back malignant cells in patients makes it challenging to implement these strategies in high-risk infertile patient groups, like cancer survivors who undergo chemotherapy or radiation treatment. The best way forward for clinical translation will be to initiate testicular and germ cell auto-transplantation in infertile patients suffering from low-risk or non-malignant diseases (like sickle-cell disease patients).

This is specifically relevant for those patients undergoing bone-marrow transplantation as they are regularly facing permanent infertility. In parallel, more efficient strategies (employing genome and transcriptome analysis tools like in situ spatial transcriptomics) need to be developed and applied to reliably detect remnants of malignant cells in cell-fractions or gonadal tissues envisaged to be transferred back into high-risk patient groups to restore fertility after cure and recovery from the disease.

Moreover, attempts to establish high throughput culture strategies in combination with miniaturized bioengineered microchip systems or using biomaterials need to be intensified, to investigate and understand biological mechanisms involved in spermatogenesis. As availability of human testicular tissue is limited for male fertility preservation research, various strategies can be adapted to overcome this technical barrier. Animal and tissue sparing multiplex systems can be developed to efficiently use limited tissue material available for various research applications [10].

Wherever normal human tissue material is not accessible, testicular tissue from well-established nonhuman primate models like macaque and marmoset monkeys can be extensively used for preclinical and translational research applications to explore testicular function [11]. Further, more advanced technological tools like artificial intelligence (AI) and big data can be efficiently implemented in reproductive biology research. Such advanced predictive modeling tools can be employed to answer various research questions, including to predict the scale or damaging impact of various degrees of gonadotoxic therapies on testicular function and fertility potential in young prepubertal cancer patients.

Thus, ex vivo models (using limited experimental samples) in combination with high-throughput advanced predictive tools can be efficiently exploited to develop clinically competent, effective, and robust strategies to investigate germ cell dynamics and to develop functional spermatozoa for infertile patients.

Correspondence to: Prof. Dr. rer. nat. Stefan Schlatt, Center for Reproductive Medicine and Andrology, Institute of Reproductive and Regenerative Biology, Albert-Schweitzer-Campus 1, Building D11, 48149 Münster, Germany, Tel: +49 251 8356099, Fax: +49 251 8354800; E-mail: stefan.schlatt@ukmuenster.de

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